Progenics Abstract

**Identification of CCR5 Coreceptor Inhibitors that Potently and Selectively Block HIV-1 Replication**

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**Background:** The CC-chemokine receptor CCR5 is a requisite fusion coreceprtor for primary HIV-1 isolates. As a seven-transmembrane G protein coupled receptor with limited tissue distribution, CCR5 represents a promising target for a new class of viral entry inhibitors. High-throughput screens for inhibitors of chemokine binding have yielded a number of CCR5 antagonists that block HIV-1 replication *in vitro*, but to date there has been no description of small molecule CCR5-targeting agents that block HIV-1 replication without antagonizing chemokine binding.

**Methods:** We performed high throughput screening of the Roche sample collection using a homogeneous cell-based Resonance Energy Transfer (RET) assay that recapitulates all stages of HIV-1 envelope glycoprotein-mediated membrane fusion. Active compounds from the primary screen and analogs thereof were evaluated for their antiviral, anti-chemokine and other properties in a cascade of secondary assays.

**Results:** Compounds were identified that specifically block CCR5-mediated, but not CXCR4-mediated, HIV-1 cell-cell and virus-cell fusion with nanomolar potency. The latter studies employed a series of env-complemented luciferase reporter viruses as well as primary HIV-1 isolates. Notably, unlike natural ligand-binding assays, this approach could identify CCR5-targeting agents that selectively block HIV-1 replication but not chemokine binding.

**Conclusions:** Using a high-throughput assay for HIV-1 membrane fusion, we identified small-molecule CCR5 inhibitors that selectively block CCR5's interactions with HIV-1. These compounds may represent promising lead candidates for further optimization as members of a new generation of antiretroviral agents.